Translation

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

10/030504

Applicant's or agent's file reference 02280PC	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB00/00918	International filing date (*day/month/year*) 07 July 2000 (07.07.00)	Priority date (*day/month/year*) 09 July 1999 (09.07.99)
International Patent Classification (IPC) or national classification and IPC C12Q 1/68		
Applicant MISEREZ, André, R.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30 January 2001 (30.01.01)	12 October 2001 (12.10.2001)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

Form PCT/IPEA/409 (cover sheet) (July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/IB00/00918

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:

pages 1-54, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☒ the claims:

pages 1-31, as originally filed

pages _____, as amended (together with any statement under Article 19

pages _____, filed with the demand

pages _____, filed with the letter of _____

☒ the drawings:

pages 1/4-4/4, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☒ the sequence listing part of the description:

pages 1-6, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1,11.

because:

☒ the said international application, or the said claims Nos. 1,11 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III

1. Claims 1 and 11 have as their subject matter a method which includes blood withdrawal or biopsy and therefore appears to be an in vivo method. The subject matter of Claims 1 and 11 therefore comes within the terms of the definition set out in PCT Rule 67.1 (iv) and no opinion is given on its industrial applicability (PCT Article 34(4)(a)(i)).

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

See separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. _____ .

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV

The present application does not satisfy the unity of invention requirement (PCT Rule 13.1).

As explained in more detail in Box V, a method for the identification of illnesses in connection with polymorphisms in the sterol-regulator element binding protein gene is novel, but not inventive. In the prior art an expert is motivated to look for mutations in sterol-regulator element binding proteins which appear in connection with changes to the cholesterol and LDL balance. Consequently, the common concept on which the present application is based - the discovering of mutations in the sterol-regulator element binding protein gene - is not inventive. Each mutation in the sterol-regulator element binding protein gene therefore describes a separate invention. The present application can therefore be divided into the complementary primer/probe sequences for the mutations discovered (Seq. Id 3; Seq. Id 7, Seq. Id 9; Seq. Id 10, Seq. Id 11, Seq. Id 12, Seq. Id 13, Seq. Id 14, Seq. Id 15, Seq. Id 16, Seq. Id 17, Seq. Id 18). Each Seq. Id therefore describes a separate invention.
However, to accelerate the procedure, the application is being examined as a whole.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	18,25	YES
	Claims	1-17, 19-24, 26-31	NO
Inventive step (IS)	Claims	18,25	YES
	Claims	1-17,19-24,26-31	NO
Industrial applicability (IA)	Claims	2-10,12-31 (1,11?)	YES
	Claims		NO

2. Citations and explanations

Reference is made to the following documents:

D1: MISEREZ ANDREW G ET AL: GENOMICS, Vol.40, No.1, 1997 SISSN: 0888-7543 cited in the application

D2: US-A-5 891 631

D3: MISEREZ: "UNI NOVA, WISSENSCHAFTMAGAZIN DER UNIVERSITÄT BASEL, Vol. 81, April 1998, XP002159139

D4: HUA XIANXIN ET AL: GENOMICS, Vol. 25, No. 3, 1995 pages 667-673, Xp000979463

D5: Yang J. et al., J. Biological Chemistry, 270, 20, May 19, 1995 pp. 12152-12161

D6: Hacia J.G. et al., Genomic Research, 8,12, 12-1998, 1245-1258

D7: Pai J. et al., J. Biological Chemistry, 273,40, October 2,1998, 26138-26148.

Documents D5 and D7 are quoted in the international search report. Copies of these are annexed (Guidelines III, PCT 7.24).

1. The subject matter of independent Claim 1 is novel (PCT Article 33(2)). A method for identifying an increased risk of illness and/or mortality dependent

on the sterol-regulator element binding protein gene is not disclosed in the prior art.

1.1 The subject matter of the independent Claim 1 is not inventive (PCT Article 33(3)).
D1 can be considered as the closest prior art. D1 describes the structure of the human gene SREBP-2 which has a key role in controlling the biosynthesis of cholesterol and the LDL metabolism. It discusses the possibility of genetic variations within this gene which could result in different LDL levels in plasma (p. 31. col. 2, p. 32 col. 1, par. 2). D1 also states that there have been no reports of any "naturally" occurring mutations in the SREBP-1 and SREBP-2 gene (p. 32, col. 1, final par.), yet at the same time refers to a publication by Yang et al. (D5) which discusses a shortened SREBP-2 protein in hamster cells (CHO) - see discussion in D5. In addition, D5 deals with the important role of the SREBP-2 gene in controlling the cholesterol metabolism. In its final paragraph on page 38, col. 2, D1 hints to the expert that variations of the SREBP-1 and SREBP-2 gene could also be found in the human genome in connection with differences in the lipid balance (as regards LDL and cholesterol balance, see also D2, p. 5, par. 2). In addition, D4, a further document on the subject of the SREBP gene, discusses the linking of SREBP-2 and SREBP-1 with cholesterol synthesis and LDL metabolism and the possible phenotypic effects which could occur (p. 672, col. 1, par. 2 and following). D3 describes the SREBP proteins and gene as possible target molecules for the treatment of hypercholesterolemia and associated illnesses (col. 2, line 64 and following). D7 describes several variants of the

SREBP gene (SREBP-1a, SREBP-1c and SREBP-2) which modulate the cholesterol and fatty acid balance of the cell (see discussion).
As a result of the discussion in D1 an expert in the art is informed of the important function of the SREBP gene (SREBP-1 and SREBP-2) and through the explanations in D3, D4, D5 and D7 the expert receives guidance and considerable motivation to look for possible mutations and polymorphisms in the SREBP genes which appear in connection with illnesses linked to the cholesterol and LDL balance. The requirements for an inventive step are therefore not met (PCT Article 33(3)).

1.2 On the same grounds, dependent Claims 2-6, 10-13, 15, 17, 19 and Claims 28 and 29 also do not meet the requirements of PCT Article 33(3)).

1.3 The subject matter of Claims 7, 8, 9, 14, 30 and 31 is novel (PCT Article 33(2)) but not inventive (PCT Article 33(3)).
In the prior art, reference is made to nucleotide variations in genes SREBP-1 and SREBP-2. The expert is therefore given cause to look for mutations in these genes. Therefore the discovery of mutations in these genes through probe, primer or restriction analysis cannot be recognised as involving an inventive step.

1.4 The subject matter of Claim 18 is novel (PCT Article 33(2) and inventive (PCT Article 33(3)).
In the prior art no connection is disclosed between SREBP-1 and SREBP-2, or the polymorphisms of this gene and the derived side effects in an HIV therapy. Consequently an inventive step can be acknowledged.

2. The subject matter of independent Claim 20, and dependent Claims 21-27 is novel (PCT Article 33(2)).

The application of DNA or RNA chip arrays is a normal method in the prior art for identifying polymorphisms. By way of example, D6 describes the application of high-density oligonucleotide arrays for the examination of heterozygote and homozygote sequence variations in the large multi-exon ATM gene (p. 1225 col. 1, par. 2). Consequently, with the facts available from the prior art (D1-D5) cited in Point 1.1 of this report, the use of DNA or RNA chips to identify mutations in the SREBP-1 and SREBP-2 genes is evident. An inventive step is therefore not necessary. Consequently, the requirements of PCT Article 33(3) are not met for the subject matter of Claim 20.

2.1 On the same grounds, the subject matter of Claims 21-24, 26 and 27 also do not meet the requirements for inventive step (PCT Article 33(3)).

2.2 The subject matter of Claim 25 cannot be recognised as involving an inventive step (see explanation in Point 1.4 of this report).

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

1. According to PCT Rule 9.1(iv), the content of lines 4-9 on page 1 is irrelevant.

2. Contrary to PCT Rule 5.1(a)(ii), the description does not cite documents D3, D5, D6 and D7 or indicate the relevant prior art disclosed therein.